

REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 1-6 and 8-16 are pending in the application. Claims 1-6 and 8-16 have been amended to address the formal matters raised in the outstanding Official Action. In addition, claim 1 has been amended to incorporate the subject matter of claim 7. Claims 7 and 17-18 have been canceled.

In the outstanding Official Action, the specification was objected to for allegedly not satisfying the requirements of 37 CFR §1.121. Applicants believe that the preliminary amendment filed with the application on October 4, 2004 satisfies the requirements of 37 CFR §1.121. The preliminary amendment replaced each of those paragraphs and properly underlined the text of the new paragraph. Nevertheless, the Examiner is invited to contact the undersigned so that this matter can be resolved if for some reason the Patent Office is of a different opinion.

The title has been amended to recite "A Method for Determining the Sequence of a Nucleic Acid Molecule".

As to the claim objections, applicants thank the Examiner for the suggestions as how to overcome the objections. Indeed, claims 1 and 5 have been amended pursuant to the Examiner's suggestions.

Claims 1-16 were rejected under 35 USC §112, second paragraph, for allegedly being indefinite. Applicants believe that the present amendment overcomes this rejection.

Claims 1-6 and 8-16 have been amended so that the claims no longer recite a narrow range or recitation that falls within a broad range or recitation. Claims 1, 2 and 3 have been amended to recite the broader recitation.

Claims 5 and 10-12 have been amended to provide antecedent basis for the terms identified by the Examiner.

As to claims 12 and 16, the phrase "such as" has been deleted from the claims.

Claim 13 has also been amended to provide antecedent basis for the terms identified by the Examiner.

Claim 14 has been amended to recite the broader range for the pH recited within the claim.

As to claim 16, the phrase "various proteins ... including" has been deleted. Applicants have utilized Markush language to identify the various proteins. Applicants believe the manner in which claim 16 has been amended is definite to one skilled in the art.

In the outstanding Official Action, claims 1-10, 13 and 16 were rejected under 35 USC §103(a) as allegedly being unpatentable over KAWASHIMA et al. in view of URDEA et al. This rejection is traversed.

KAWASHIMA et al. is directed to a method of nucleic acid sequencing. KAWASHIMA indicates that different nucleic acid molecules present at different locations can be sequenced in parallel. In particular, KAWASHIMA utilizes primers that are annealed to the nucleic acid molecules. Each location can then be provided with a nucleic acid polymerase and a nucleotide. It can then be determined whether or not the nucleotide has been used in primer extension and the process can be repeated.

The disclosure of KAWASHIMA differs from the subject matter of amended claim 1 in that KAWASHIMA fails to specify that the label is neutralized after step d). At page 6, lines 25-26 of KAWASHIMA, KAWASHIMA discusses the removal of labels. However, the passage at page 6, lines 18-27 of KAWASHIMA states

"The present invention allows labeled nucleotides to be incorporated in a stepwise manner in a nucleic acid molecule via primer extension. However, the presence of one labeled nucleotide in the molecule does not prevent other labeled molecules from being detected (even if adjacent labeled nucleotides are the same). Thus, unlike many prior art parallel sequencing methods, such as those disclosed in WO93/21340 and DE-A-4141178, there is no need to remove a label from polynucleotide chain before a further labeled nucleotide is added (although in some embodiments it may be desired to remove labels periodically). A plurality of labels can therefore be incorporated into a nucleic acid molecule via primer extension and can be detected in situ."

In other words, one of the advantages of the method of KAWASHIMA is that there is no need to remove a label from a nucleotide chain. If labels are removed, they are only removed periodically, not after each detection step.

Contrary to the assertions of the Official Action, the passage at page 18, lines 9-26 merely states that after several steps of sequencing that it may be desirable to remove a label. Thus, KAWASHIMA does not disclose or suggest claimed step d) as presently recited. Rather, KAWASHIMA leads one skilled in the art away from the claimed invention.

Indeed, the present specification even discusses KAWASHIMA in detail on page 2 as follows:

"The method involves primer extension using labeled nucleotides. Mixtures of labeled/natural nucleotides containing labeled nucleotides of <50%, <20% or <10% of the total are mentioned. The reason for using such mixtures is to reduce costs and also possibly to reduce quenching effects if certain labels are used where signals from such labels interfere with each other. There is no attempt to remove the signal incorporated. Rather, the signal accumulates for each additional incorporation. The fluorescence variant of this method cannot be expected to work for longer sequences since the sensitivity will successively be reduced as the total signal increases."

In an effort to remedy the deficiencies of KAWASHIMA for reference purposes, the Official Action cites to URDEA. However, URDEA relates to labelled nucleotides where the fluorescent label is linked to the nucleotide with a cleavable disulfide linker. URDEA does not relate to sequencing methods.

In view of KAWASHIMA and URDEA, one skilled in the art would not have a reason or expectation that removing the label after every detection step would provide a method as claimed by which sensitive sequencing of longer sequences would be possible.

Thus, in view of the above, applicants respectfully submit that the proposed combination of KAWASHIMA in view of URDEA fails to disclose or suggest the claimed invention.

The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S.Ct. at 1731.

Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.*

As neither publication provides a reason for combining and modifying the publication to obtain a method as recited in step d) of claim 1, applicants respectfully submit that the proposed combination of KAWASHIMA in view of URDEA fails to render obvious the claimed invention.

Claims 11-12 are rejected under 35 USC §103(a) as allegedly being unpatentable over KAWASHIMA in view of URDEA and further in view of VERDINE. This rejection is traversed.

As noted above, applicants respectfully submit that the proposed combination of KAWASHIMA in view of URDEA fails to render obvious the claimed invention. The Official Action cites to VERDINE for the proposition that VERDINE teaches the attachment of molecules to nucleotides using disulfide links. However, VERDINE fails to render the deficiencies of KAWASHIMA and URDEA for reference purposes. There is no recognition or suggestion of removing a label from a nucleotide chain as recited in the claimed invention.

Thus, applicants request that the rejection be withdrawn.

Claims 1 and 14 were rejected under 35 USC §103(a) as allegedly being unpatentable over KAWASHIMA in view of URDEA and further in view of UEMORI. This rejection is traversed.

UEMORI relates to a DNA polymerase. Thus, UEMORI does not disclose or suggest a method as recited in the claimed invention.

Thus, applicants ask that the rejection be withdrawn.

Claims 1 and 15 were rejected under 35 USC §103(a) as allegedly being unpatentable over KAWASHIMA in view of URDEA and further in view of LEE. This rejection is traversed.

LEE discloses a method for primer extension using fluorescent compounds for labels. LEE does not remedy the deficiencies of KAWASHIMA and URDEA for reference purposes.

There is no teaching of a method utilizing step d) as recited in the claimed invention.

In view of the above, applicants ask that the rejection be withdrawn.

Claims 1 and 7-8 were provisionally rejected on the grounds of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 33 and 34 of copending application No. 10/529,352 in view of KAWASHIMA et al. This rejection is traversed.

Pursuant to MPEP §804 (I) (B)1., if a "provisional" non-statutory obviousness type double patenting rejection is the only rejection remaining in the earlier filed of two pending applications, while the later-filed applicant is rejectable on other grounds, the Examiner should withdraw that rejection to permit the earlier-filed application to issue as patent without a terminal disclaimer. As the present application was filed earlier than copending application No. 10/529,352, applicants note that the double patenting rejection should not prevent the present application from allowance and passage to issue. Thus, as applicants believe that all the rejections identified above have been properly addressed, applicants believe that the present application is in condition for allowance at the time of the next Official Action.

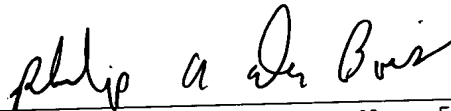
In view of the present amendment and the foregoing remarks, therefore, applicants believe that the present

application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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